Long-term anticoagulation in questions and answers

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How do we prepare a patient on oral anticoagulation with vitamin K antagonists (VKAs) for cataract surgery? Patients treated with VKAs can undergo surgery when the value of an international normalized ratio (INR) is 2 or lower on the day of surgery. Cataract surgery is associated with low risk of bleeding complications (similarly to most dental procedures). The 2014 European Society of Cardiology (ESC) guidelines on preparing patients for noncardiac surgery and the 2008 guidelines of the American College of Chest Physicians clearly indicate that the cataract surgery, and more specifically, preprocedural anesthesia, is not associated with an increased risk of permanent vision impairment caused by hematoma. Prior to cataract surgery, bridging therapy with a low-molecular-weight heparin (LMWH) should not be used as a routine procedure because it is associated with a 2- to 3-fold higher risk of bleeding without difference in the risk of thromboembolism estimated at lower than 1%. Moreover, the withdrawal of VKAs for at least 5 to 8 days and subsequent dose titration to return to therapeutic INRs that takes even up to a few days after surgery disturb the stability of long-term anticoagulation and may also impose a greater risk on thromboembolic complications in next weeks, especially among high-risk patients such as those with an implanted prosthetic mitral valve and numerous comorbidities. Therefore, a patient before cataract surgery should not be treated in the same way as before an open abdominal surgery or neurosurgery. Nowadays, more and more cataract centers perform surgery in patients with INR values of about 2 and safely manage their patients without switching them to LMWH. The decision of whether to continue anticoagulation in the preoperative period is at the discretion of the performing surgeon supported by an internist, but VKAs should not be routinely withdrawn because of cataract surgery because this is not recommended by the current guidelines.

It is worth mentioning that patients taking non-vitamin K antagonist oral anticoagulants (NOACs) should discontinue these drugs 24 to 36 hours before surgery. It is not recommended to use bridging anticoagulant therapy in patients on NOACs.

Which anticoagulants should be used for patients with atrial fibrillation and cancer? In the management of patients with atrial fibrillation (AF) and cancer, VKAs or NOACs can be used for stroke prevention. However, the effectiveness and safety of treatment with NOACs in this specific group of patients are poorly documented because these patients have not been included in large randomized clinical trials on the use of NOACs in AF. However, clinical practice shows that NOACs are well tolerated by most cancer patients in good general condition, receiving outpatient cancer treatment, and with low-to-moderate bleeding risk, and not taking antifungal drugs or cyclosporine. In everyday practice, however, LMWH are mostly used in patients with venous thromboembolism (VTE), and not with AF, except when such management is planned only for a short time and because of invasive procedures, nausea, vomiting, or diarrhea, and other complications of an underlying disease. The effectiveness of LMWH (particularly at prophylactic or moderate doses) in AF, especially in high-risk patients is unknown; however, in high-risk cancer inpatients with elevated risk of bleeding LMWH should be considered. Anticoagulation strategy should be individualized in cancer patients especially if both bleeding and thrombosis risks are high.

Is anticoagulant therapy beneficial for a patient with a survival probability of 0.5 to 1 year, who is on palliative treatment because of heart failure with AF? Is it reasonable to maintain this patient on such a therapy? There has been no clinical trials regarding patients with such a bad prognosis requiring anticoagulation. The decision should be based on the classic risk scores, such as the CHA_2DS_2-VASc score to assess the thromboembolic risk

in AF and the HAS-BLED score or others to assess the bleeding risk, but it has to be made on individual basis. Continued anticoagulant therapy may be considered in patients at high risk of thromboembolic events if kidney and liver function is satisfactory and there is no anemia or recurrent clinically relevant bleeding, because most patients would choose the perspective of living 1 year without disabling stroke. It is suitable to administer a reduced dose of a NOAC in most such cases, namely, dabigatran (2×110 mg/d) or apixaban (2×2.5 mg/d), which are currently recommended as the safest options in patients with AF at high risk of bleeding.

How to treat patients in whom INR cannot be measured because of older age, disability, inability to follow complex instructions, or refusal to use NOACs due to cost? Should LMWH or acetylsalicylic acid (ASA) be started? We should aim at minimizing the number of patients requiring long-term anticoagulation who are not treated according to the current guidelines in the European Union, because other therapeutic options have minimal or uncertain effectiveness. In the United Kingdom and in the entire European Union, the use of ASA is not recommended for the prevention of stroke in AF since September 2016; the effectiveness of this agent is very limited with a 2-fold higher risk of bleeding, particularly from the gastrointestinal tract. Currently, it is unknown whether LMWH could decrease the risk of stroke because this issue has not been systematically studied in patients with AF so far. The use of LMWH is rather a short-term option (eg, in the perioperative period). The majority of patients will hardly accept the many years with everyday subcutaneous injections. From my experience, LMWHs at prophylactic or intermediate doses given once daily (the half-time of this drug is about 12 hours) do not protect against stroke, especially if the CHA_2DS_2-VASc score is high, and they are not well tolerated by patients (injections are administered for many weeks). Moreover, they are not even recommended by the guidelines as a therapeutic option in AF. The 2012 ESC guidelines have recommended a combination therapy of ASA plus clopidogrel as an alternative to anticoagulants, but such an option is rarely used in practice and it disappeared in the 2016 ESC guidelines for AF. Undoubtedly, if a patient with AF refuses the treatment with any NOACs, a physician should note that down in the patient's medical records and consider administering ASA instead of oral anticoagulation as this option is supported by more reliable evidence than LMWHs. The latter drugs could be used, if acceptable, in patients following VTE.

Finally, several measures to improve anticoagulation control in patients on VKAs should be undertaken, starting from dietary advice, review of potentially interfering comedications, etc.

Which anticoagulants, novel or old, are safer for patients with gastrointestinal bleeding? If bleeding was major and its cause was unknown (eg, not during treatment with VKA or nonsteroidal anti-inflammatory drugs [NSAIDs], especially cyclooxygenase-1 inhibitors), a NOAC, often at a reduced dose, should be initiated. The 2016 ESC guidelines recommend reduced doses of NOACs in AF patients at high risk of gastrointestinal bleeding. Based on large clinical studies in patients with AF, experts recommend dabigatran at a dose of 2×110 mg/d or apixaban at a dose of 2×5 mg/d or 2×2.5 mg/d, or rivaroxaban 15 mg/d as the options to be considered. Apixaban and lower doses of dabigatran administered to AF patients do not increase the risk of gastrointestinal bleeding compared with warfarin. In patients with persistent bleeding, especially those older than 70 years (eg, with diverticulosis), the safest option in my opinion would be apixaban at a dose of 2×2.5 mg/d. Even if bleeding occurs during the use of apixaban, then the patient will rather not be able to take anticoagulants. Patients with previous gastrointestinal bleeding should avoid the use of NSAIDs (paracetamol can be given instead as an antipyretic or analgesic agent), because in elderly patients these drugs are the most common modifiable risk factor for bleeding. Proton pomp inhibitors should be added to an anticoagulant to reduce upper gastrointestinal bleeding.

Is there an alternative for oral anticoagulants in patients with prosthetic heart valves? Can we introduce a long-term treatment with LMWH, and if yes, at what doses? How to manage a patient with a prosthetic heart valve, who takes acenocoumarol or warfarin and has an INR in the range of 8 to 11, despite previously stable values for many years? There is no alternative to the long-term use of VKAs in patients with prosthetic heart valves, either the currently implanted ones or those implanted in the past. INR may be optimized by diet, review of interfering drugs (including over-the-counter medications, such as herbal remedies), self-monitoring, etc. Two to three days on antibiotics or with gastrointestinal symptoms leading to diarrhea and reduced food intake could result in an increase of INRs above 5. With unstable INR values, it is most important to check for signs or symptoms of bleeding and measure INRs every 1 or 2 weeks, if feasible. Good clinical tolerance of fluctuating INR values is a good prognostic factor in such patients. INR should then be measured more often, and when the requirement for a VKA is low (≤2 mg/d of acenocoumarol), low doses of oral vitamin K could be added—then the requirement for the VKA increases and INR values stabilize. However, a specialist should help manage such patients.

What are the most frequent adverse effects of acenocoumarol and warfarin, except bleedings? Are severe skin reactions, vasculitis, and chronic and generalized

pruritus common adverse effects of a long-term use of VKAs? When a drug change is indicated in such cases? Skin lesions, hair loss, and headaches can be the adverse effects of VKAs if other causes are excluded or unknown. In 2% of cases, elevated levels of liver enzymes could be observed, especially in patients taking other hepatotoxic agents (eg, amiodarone) or having concomitant liver diseases. These symptoms are an indication for a drug switch if only possible. For example, there is no need for patients with nonvalvular AF to experience the side effects of VKAs if they can use NOACs instead, which are a preferred option for this indication.

Can dabigatran be continued after an episode of gastrointestinal bleeding? I prescribed dabigatran at a dose of 150 mg bid to a patient with a high risk of VTE complications (based on the CHA_2DS_2-VASc score) and an estimated glomerular filtration rate exceeding 60 ml/min/1.73 m^2. The patient had no previous gastrointestinal symptoms. After a few months of dabigatran use, the patient suffered a massive upper gastrointestinal hemorrhage, which required a transfusion of a few packed red blood cell units. Endoscopy revealed duodenal ulcer (no other symptoms except bleeding). The etiology of the ulcer could not be determined (whether it was the use of NSAIDs or *Helicobacter pylori* infection), but the patient received treatment for *Helicobacter pylori* eradication in case it was present. Obviously, the risk of thromboembolic complications remained the same after the bleeding. Can we reinstitute dabigatran treatment on endoscopic confirmation of ulcer healing? What anticoagulant treatment should be used during the minimum of 6 to 7 weeks of ulcer treatment? Beside the assessment of thromboembolic risk, also the bleeding risk should be assessed in patients with AF. Patients with low bleeding risk (likely in the case presented) will require a reduced dose of NOACs after an episode of bleeding. According to indirect analyses of randomized trials and recent registries from the United States and Denmark, apixaban appears the safest oral anticoagulant in such cases. The risk of gastrointestinal bleeding is significantly higher (by about 20%) in AF patients on dabigatran and rivaroxaban than in those on warfarin (according to the results of the RE-LY and ROCKET-AF trials), which is associated with the presence of an active form of a NOAC in the gastrointestinal tract. In this particular case, I would opt for apixaban 2 × 2.5 mg/d although a strong indication to reduced doses is when the patient meets 2 of the 3 criteria: body mass ≤60 kg, age ≥80 years, and serum creatinine levels ≥133 μmol/l.

If the patient cannot afford apixaban, dabigatran or rivaroxaban can be introduced again usually after 4 weeks (and no later than 6 to 8 weeks). As bridging therapy, LMWH is usually used at intermediate doses (longer use of moderate doses or termination of the therapy may increase the risk of ischemic stroke) and always with a proton pump inhibitor. NSAIDs (including ASA) are contraindicated as they are associated with several episodes of upper gastrointestinal bleeding, including in patients on NOACs.

Which analgesic or antipyretic can be given to a patient on warfarin, acenocoumarol, dabigatran, or rivaroxaban treatment? Paracetamol at a dose of up to 2 g/d is considered safe in patients with normal liver function. Also a combination therapy of paracetamol with codeine or tramadol can be used. Of note, higher doses of paracetamol administered for 3 to 5 days increase INRs and might destabilize anticoagulation with VKAs. Patients on warfarin, acenocoumarol, dabigatran, or rivaroxaban treatment should not be given NSAIDs, although most patients tolerate the short-term use of cyclooxygenase-1 inhibitors (especially patients with low bleeding risk). Therefore, the use of anticoagulants is not an absolute contraindication to the use of NSAIDs. However, such treatment should be administered with caution.

How does a short-term use of paracetamol, tramadol, or NSAIDs (administered for example during infection or for acute pain) affect VKA treatment? These drugs have a minor effect on VKA treatment; only paracetamol >2 g/d for a few days increase INRs. By inhibiting platelet aggregation (via a mechanism similar to that of ASA), NSAIDs increase the bleeding tendency if a blood vessel is already damaged (eg, because of gastritis). In elderly people on anticoagulant treatment, it is always necessary to add a proton pump inhibitor, even if NSAIDs are prescribed only for a few days.

What is the pharmacologic management in case of bleeding in patients receiving rivaroxaban/dabigatran as prevention of thromboembolism during AF? After the episode of bleeding, should a NOAC be continued at modified doses or should it be changed to a VKA along with a recommendation for more careful monitoring? After each bleeding episode in a patient using NOAC, the severity and cause of bleeding should be assessed. Bleeding tendency observed prior to anticoagulation initiation should be excluded (bleedings, such as menstrual bleedings, are often worsened by anticoagulant therapy). Creatinine clearance should also be assessed and compared with the previous values, as well as complete blood cell count (particularly the platelet count). The use of other drugs (especially NSAIDs) and bleeding episodes in the past should be recorded. Only serious bleeding should prompt a decision about the possible change of treatment, so bruises of 2 to 3 cm on the extremities are in most cases the "price" for stroke prevention, and their presence should not be an indication for a change in therapy. Such a change is indicated when the thromboembolic risk is high (similarly as in the case of VKA therapy). What is necessary at all times is a diagnostic workup and treatment of the underlying organic cause

(especially if it is located in the large intestine or urinary system). Bleeding from these sites can be a predictor of cancer, among other diseases, and it is wrong to assume that bleeding during anticoagulant therapy originates only from a healthy organ and was caused only by the use of an anticoagulant drug. Indications for a change in therapy after a serious bleeding episode include periodic worsening of renal function (which may favor the accumulation of a drug, particularly dabigatran), features of liver function impairment, low platelet count, etc. According to comparative trials (without head-to-head comparisons), upper and lower gastrointestinal bleeding occurs more often among patients treated with dabigatran and rivaroxaban (mainly due to the presence of high amounts of an active drug in the gastrointestinal tract) than in those treated with warfarin, while it occurs at a similar rate compared with patients treated with apixaban (which is also eliminated by the kidneys only in approximately 25%, and is considered a safer option when creatinine clearance is low, especially 30–40 ml/min). So if we are able to exclude the modifiable risk factor for bleeding (particularly the use of other drugs, mainly NSAIDs) and if the kidney function and platelet count are normal, we should reassess the bleeding risk. Then, we should either use a reduced dose of the same drug or switch anticoagulants. Many experts recommend reducing the dose of NOAC among patients after serious bleeding and among most patients older than 75 years; dabigatran 2 × 110 mg/d at such age is currently recommended by the ESC. If bleeding recurs (eg, gastrointestinal bleeding of unknown cause), a reinitiation of VKA therapy with regular INR monitoring and target INR values of 2 to 2.5 should be considered. After an episode of serious bleeding, LMWH should be used for a short time, usually up to 4 weeks, especially when additional invasive diagnostic procedures are planned.

As a primary care physician, I frequently encounter patients asking to prescribe them LMWH instead of ASA before an elective procedure, such as dilation and curettage, colonoscopy with polypectomy, or cataract surgery. Are there any new recommendations for these particular patients? LMWH should not be used as bridging therapy in patients on long-term ASA treatment for the prevention of cardiovascular events. First of all, LMWH do not inhibit platelet function. Secondly, most invasive procedures, including those with high bleeding risk (eg, cardiac surgeries), can be performed in patients taking ASA or other NSAIDs. ASA should not be discontinued before, for example, a cataract surgery in elderly patients after recent myocardial infarction (ie, with a strong indication to using ASA). Thirdly, LMWHs increase the risk of perioperative bleeding, and given at a prophylactic dose, they will surely not protect against myocardial infarction. Finally, if ASA is used for secondary VTE prevention long after the primary incident, which is more and more common after discontinuing anticoagulation, then the withdrawal of ASA does not require prophylaxis with LMWH. It is necessary to ensure proper hydration, use compression therapy (if these are complications of deep venous thrombosis), and ensure that the patient is mobilized as soon as possible. The use of LMWH should be limited to patients treated with anticoagulants, who have a high or moderate risk of thromboembolism but low risk of bleeding (or lower than the risk of peripheral embolus or thrombosis, especially on the prosthetic heart valve). Of note, up to 1% of the patients treated with LMWH can develop heparin-induced thrombocytopenia, which is associated with a high risk of thromboembolic complications.

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